B1 Cont overexpression of these genes as well as any other disease involving SKI-1 activity, it is contemplated that any inhibitor of SKI-1 would be useful in their treatment

2. On page 27, please amend Paragraph 1, as follows:

Genetic and biochemical evidence indicates that SKI-1/S1p is the protease that cleaves sterol-regulatory element-binding proteins (SREBPs) which functions to control lipid biosynthesis and uptake in animal cells { Sakai, J. et al. (1998) Molecular Cell 2, 505-514; Cheng, D. et al. (1999) J. Biol. Chem. 274, 22805-22812; Toure, A. et al. (1999) In: Peptides for the Now Millennium: Proceedings of the 16th American Peptide symposium}. SKI-1 and SREBPs play critical roles in the feedback pathways by which cholesterol suppresses transcription of genes encoding HMG CoA reductase and other enzymes of cholesterol biosynthesis as well as the low density lipoprotein (LDL) receptor. A SKI-1 inhibitor would be of use under clinical conditions in which there is not sufficient down regulation of SREBP dependent transcription by sterols. For example, in the Nieman-Pick group of diseases a high sphingomylin content of cells leads to an increase in proteolysis of SREBP-2 and a subsequent increase in cholesterol biosyntheses { Scheek, S. et al. (1997) Proc. Natl. Acad. Sci. USA 94, 11179-11183; Spence, M.W., and Callahan, J.W. (1989) Spingomyelin-cholesterol lipidoses: The Nieman-Pick Group of Diseases. *In The Metabolic Basis of Inherited Disease*) Scriver, C.R., Beaudet, A.L., Sly, W.S., and Valle, D., editors), McGraw-Hill Publ. Co., 6th edition, chapter 66, 1655-1676; Sviridov, D. (1999) Histology & Histopathology 14 (1): 305-319 }. Perhaps of greater significance, nuclear SREBP-1c protein levels were significantly elevated in mouse models for non-insulin dependent diabetes, *ob/ob* and aP2 SREBP-1c mice, which

B2

was associated with elevated mRNA levels for known SREBP target genes involved in the biosynthesis of fatty acids (Schimomura, I. *et al.* J. Biol. Chem. 1999; 274:30028-30032).

3. On page 50, please amend the last paragraph to read:

Results of immunocytochemistry performed in mouse lacrimal glands provides evidence for the presence of SKI-1 and APP in the same cells types, including intralobular duct epithelial cells and some acinar cells (Fig. 26). The finding of SKI-1 in the lacrimal gland suggests the possibility of developing a diagnostic assay analyzing tears; perhaps based on two-dimensional polyacrylamide gel electrophoresis for disease diagnosis { Moley, M.P. et al. (1997) Electrophoresis 18, 2811-2815; Glasson, M.J. et al. (1998) Electrophoresis 19, 852-855; Grus, F.H., and Augustin, A.J. (1999) Electrophoresis 20, 875-880; Iskeleli, G. et al. (1999) CLAO Journal, 25:101-104;

4. On page 72, please amend Example 1, 3. to read as follows:

Seidah, N.G., Mbikay, M., Marcinkiewicz, M., & Chretien, M. (1998) in *Proteolytic and Cellular Mechanisms in Prohormone and Proprotein Processing,* ed. Hook, V.Y.H. (R.G. Landes Company, Georgetown, TX), pp. 49-76.

5. On page 72, please amend Example 1, 4., to read as follows:

Ling, N., Burgus, R., & Guillemin, R. (1976) *Proc. Natl. Acad. Sci. USA* **73**, 3942-3946.

6. On page 74-75, please amend Example 2, 10., to read as follows:

Seidah, N.G., Mbikay, M., Marcinkiewicz, M. and Chretien, M., The mammalian precursor convertases: paralogs of the subtilisin/kexin family of calcium-dependent serine proteinases. In: Hook, V.Y.H. (Ed.), Proteolytic and Cellular Mechanisms in Prohormone and Proprotein Processing. R.G. Landes Company, Georgetown, TX, USA, 1998, pp. 49-76.

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7. On page 75, please amend Example 2, 13., to read as follows:

Hallenberger, S., Moulard, M., Sordel, M., Klenk, H.D., and Garten, W. – The role of eukaryotic subtilisin-like endoproteases for the activation of human immunodeficiency virus glycoproteins in natural host cells. – Journal of Virology 1997;71; 1036-1045.

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8. On page 77, please amend Example 3, 4th reference, to read as follows:

Ling, N., Burgus, R., and Guillemin, R. (1976) *Proc. Natl. Acad. Sci. USA* **73**, 3942-3946.

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9. On page 78, please amend Example 3, 21st reference, to read as follows:

Rittenhouse, J., and Marcus, F. (1984) *Anal. Biochem.* **138,** 442-448

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10. On page 79, please amend Example 3, 35th reference, to read as follows:

Zhong, M., Munzer, J.S.., Basak, A., Benjannet, S., Mowla, S.J., Decroly, E., Chretien, M. and Seidah, N.G. (1999) J. Biol. Chem. 274:33913-33920.

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No fees are believed necessary to enter this amendment. However, if any fees are necessary, please charge Deposit Account 17-0055.

Respectfully submitted,

Nabil G. Seidah, <u>et</u> <u>al</u>.

October 18, 2001

By: [signature]

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